

## II

# CLINICAL OBSERVATIONS ON THE TREATMENT OF GONORRHŒA IN THE MALE WITH SULPHANILAMIDE\*

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LADIES AND GENTLEMEN,—It would, I am sure, be hardly courteous of me to inflict on you, at this time of day, the tedium of my attempt to describe the compounds generally called “Sulphanilamide”; to give the history of their introduction to medicine, or to refer to their now well-known successes in bacterial infections other than gonococcal. We owe to Domagk (1935) the sulphanilamide compound, Prontosil; and the observations which I have the privilege of submitting to you now have all been made with the Bayer product, Prontosil.

Sulphanilamide was bound to be given trials in gonococcal infections. Delay in doing so was due, I think, to the fact that all doctors constantly engaged in the care of gonococcal patients were firmly possessed of a hard-won scepticism about any drug being of any help in the treatment of gonorrhœa. But after Buttle and co-workers report (*Lancet*, 1936) of the efficacy of sulphanilamide in experimental meningococcal infections in mice, the ball was set rolling. My own use of Prontosil in gonorrhœa in the male was for long haphazard and half-hearted—eventually, however, I gained the impression that in more cases than would be reasonable to put down to chance, Prontosil, given sometimes by mouth, sometimes intravenously, had notably shortened the period of treatment. It had become worth while to give it a more orderly trial—in the course of which support and encouragement came from the work of Dees and Colston (*Journal of the American Medical Association*, May, 1937).

I must give some account of the background against which my trials with Prontosil were shown up in the

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V.D. Clinic of the Seamen's Hospital, Royal Albert Docks. The patients, as a whole, had changed for the better. They are all, this last year, in work and hard at work, healthy, well-fed, good-humoured, and nearly all under thirty years old. Treatment for gonorrhœa has been a once-daily urethral lavage, under 3 feet of pressure, anterior and posterior always, with not stronger than 1 : 15,000 Potassium Permanganate warm solution, and the majority have had this lavage on five days a week only. Enlarged tender prostates were massaged for diagnosis only, never for treatment. No dilator was used and no massage over sounds. No instillations of silver salts. Acriflavine, gr.  $\frac{1}{2}$  t.i.d. by mouth, was given to all. At the least it colours the urine orange-yellow, and it gave deep satisfaction to them all.

No dieting. The few teetotallers were advised to drink plenty of water; the others were encouraged to drink beer rather than other forms of alcohol. Beer means, at least, a larger water intake. It also means the cheerful companionship of fellows, a forgetting of gonorrhœa, and an escape from nagging questions, especially those of women.

I may be allowed now to get in first with the criticism that perhaps a change in so easy-going a rule and provenance could hardly make things worse and might easily bring improvement.

So much for the background: now for the results produced by Prontosil.

My observations are on selected cases of gonococcal urethritis in the male.

They are selected only in so far as they fulfil *all* of five conditions. They are all first infections; none had had any previous treatment; the gonococcus was demonstrated microscopically in smears in all either before or in the course of Prontosil treatment; no other bacterial infection of the urethra was detected; and, lastly, all attended for the fixed period of observation and examination after cessation of treatment until formal discharge from the clinic.

Within these limits of selection the cases are consecutive. They fall chronologically into three successive groups. A scheme of treatment once begun was not altered for any one patient: therefore the last few cases in the first group overlapped the first few in the second

group, and the last few in the second overlapped the first few in the third.

Cure should mean complete disinfestation. As I know of no practicable means of determining this within any reasonable limit of time, I shall not speak of cure. The tests for formal discharge from the clinic were : (1) After complete cessation of all treatment for seven days an intradermal injection of 0.5 c.c. of undiluted Corbus-Ferry soluble toxin (gonococcus) ; (2) after one more week, the patient being reminded that he might still drink his beer, and a little more, nothing abnormal on urethroscopy of anterior urethra, nor on digital examination per rectum : a clear urine at time of examination ; and (3) the first urine passed that (fourteenth) morning after a night's sleep revealing, on microscopical examination of centrifuged deposit, no, or only a few, polymorphonuclear leucocytes, and no gonococci. Thus the patient was observed and examined fourteen days after complete cessation of treatment.

A general review of the cases will show a transition from Prontosil as an adjuvant to lavage ; through decrease of lavage and increase of Prontosil ; to Prontosil alone and again increased.

*Group 1. 30 Cases.*—Each case received 2 gm. of Prontosil Album per day by mouth (one  $\frac{1}{2}$  gm. 4 times a day), for 6 days a week, and on 5 consecutive days a week a urethral lavage ant. and post. of Pot. Permanganate 1 : 15,000 warm solution.

15 cases were infections (I.) within 7 days. Treatment (T.) 2 to 4 weeks ; 2 weeks' observation (O.).

5 I. 10 to 14 days—one had enlarged, tender prostate (P.) ; T. 2 to 5 weeks ; 2 weeks' observation.

10 I. 10 to 21 days ; 4 P. ; T. 3 to 6 weeks ; O. 2 weeks.

As soon as the patient was observed to be getting well the amount of Prontosil was reduced, so that for all these 30 during the last week of treatment the Prontosil Album was reduced to  $1\frac{1}{2}$  gm. per day—but the daily lavage was continued. Amounts taken varied from 21 gm. in 2 weeks to 69 gm. in 6 weeks. It is to be noted that after every 6 days (12 gm.) the patient had 24 hours clear without any Prontosil. Only 1 case had slight nausea and loss of appetite for the first 2 days—passing off without stopping the drug. Otherwise no signs suggesting poison-

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ing were observed. Prontosil Album had shortened the period of treatment, especially so in infections not older than 7 to 10 days.

*Group 2. 39 Cases.*—1 gm. Prontosil Album by mouth 3 times a day (3 gm.) on 6 days a week ; and on 3 days a week an intravenous injection of 5 c.c. of 5 per cent. Prontosil soluble, followed immediately by anterior and posterior lavage, 1 : 15,000 Pot. Permang. warm solution, *i.e.*, 3 lavages a week only.

20 I. within 7 days ; T. 10 days to 3 weeks ; O. 2 weeks.

8 I. 10 to 14 days ; P. 2 ; T. 10 days to 3 weeks ; O. 2 weeks.

11 I. 21 to 28 days ; P. 4 ; T. 2 to 3 weeks ; O. 2 weeks.

Here again patients received during the last week of treatment only 1½ gm. of Prontosil Album by mouth ; but injection and lavage were continued. Amount taken by mouth varied from 30 gm. in 10 days to 69 gm. in 3 weeks, with 1 clear day without drug every 6 days (18 gm.) in addition to injected Prontosil.

Number of injections varied from 5 to 9. 5 cases only complained of nausea and loss of appetite during the first 2 to 4 days of treatment, passing off without stopping the drug. The injections were given intravenously because of previous observations on cases who had received it intramuscularly in the wards of the hospital for streptococcal infections—they all had complained of severe pain at the site of injection.

In 7 cases the first intravenous injection produced flushing and vomiting, and in one a sensation of dizziness and faintness, but subsequent injections produced in them only slight flushing.

In these 39 cases there was again a reduction in period of treatment, more marked in the earlier infections.

*Group 3. 30 Cases.*—No urethral lavage. They received 1 gm. 3 times a day of Prontosil Album (3 gm.) by mouth on 6 days a week, and on 3 days a week an injection of 10 c.c. of 5 per cent. Prontosil.

The injection dose of Prontosil soluble was thus doubled. It was given deep subcutaneously and found to cause little or no pain. The first injection, however, was always 5 c.c. only, and in course of treatment there was no tailing off.

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### *Of these 30 Cases :*

11 I. within 7 days ; T. 6 days, *i.e.*, 18 gm. of Prontosil Album by mouth, one 5 c.c. and two 10 c.c. injections of 5 per cent. Prontosil soluble ; 2 weeks' O.

6 I. within 7 days ; T. 10 days, *i.e.*, 24 gm. Prontosil Album by mouth, with 1 clear day without drug after 6 days (18 gm.) and one 5 c.c. injection and four 10 c.c. injection of 5 per cent. Prontosil soluble ; O. 2 weeks.

1 I. within 3 days. This case was a bad failure. When first seen digital examination P.R. revealed nothing abnormal, free pus from urethra. Seen on third day he reported no discharge and his urine was clear. He had then had 8 gm. of Prontosil Album by mouth and one 5 c.c. injection of Prontosil soluble 10 per cent. P. Album was continued by mouth, 1 gm. t.i.d., and he was given by injection 10 c.c. Prontosil soluble 5 per cent. Seen 2 days later, *i.e.*, after a further 6 gm. by mouth (14 gm.), he looked very ill ; he complained of complete loss of appetite, severe headache, constant nausea. He had now a very large left epididymo-orchitis, and per rectum could be felt a large tender hot prostate, and a large tender seminal vesicle. His temperature was 102.4° F.

Age 55, very recently a widower, and, he said, hitherto a respected and respectable man ; a life-long teetotaler ; volubly deploring the 2 hours' irregularity that had resulted in his urethritis. His mental distress from the beginning had been obvious.

A blood count showed a slight leucocytosis of 12,000, reduction of polymorphonuclears to 50 per cent., and 12 per cent. transitionals. No changes in the red cells. There is here a suggestion of harmful effect on bone marrow tissue. He received no further Prontosil, and headache and nausea vanished, appetite returned and 10 days later his blood count was normal. He was not admitted to hospital.

1 case I. 21 days ; P. enlarged and tender ; T. 10 days ; O. 2 weeks.

4 cases I. 22 to 24 days ; in all P. enlarged and tender ; T. 14 days ; O. 2 weeks. (36 gm. per os, 1 day clear after each 6 days (18 gm.) ; one 5 c.c. and five 10 c.c. Prontosil injection, 5 per cent.)

3 cases I. 28 to 30 days ; no palpable enlargement of prostate ; T. 18 days ; O. 2 weeks. (42 gm. per os, 1 day

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clear after each 6 days (18 gm.) ; one 5 c.c. and seven 10 c.c. Prontosil injection, 5 per cent.)

4 cases I. 21 to 25 days. No palpable prostatitis, all failures after 21 days' treatment, during which time they received 54 gm. P. Album by mouth, with 1 clear day after each 6 days (18 gm.) ; and by injection one of 5 c.c. P. sol., 5 per cent, and eight of 10 c.c. P. sol., 5 per cent.

In all 4 eventual failures followed on an early apparent success. After 2 to 4 days discharge had ceased, and urine passed in clinic was clear ; but after that continuous pus and heavy threads in urine, in which intra- and extra-cellular gonococci were easily found. At this point no palpable prostatitis was found. After washing out the anterior urethra with sterile normal saline solution, urethroscopy revealed in 2 cases a very extensive and well-defined littritis. In the other 2 all the anterior urethra was pale, œdematous, with complete obliteration of striæ. None of these 4 had shown any symptoms of Prontosil poisoning and their blood counts were normal.

There are thus 5, so far observed, failures out of 30 cases treated with Prontosil only.

Time no doubt will reveal more. There are so far no return cases, and these Prontosil trials were begun on the perhaps ominous date, April 1st of this year.

A very frequent observation has been that the first effect of Prontosil treatment is an apparent increase in the number of intra- and extra-cellular gonococci found in the urethral pus or threads. The gonococci have either undergone rapid multiplication or they have been excreted from the tissues more rapidly. As Prontosil treatment proceeds so various changes in shape and staining of the gonococci can be observed, till suddenly, often 24 to 36 hours after first Prontosil dose, all gonococci vanish.

Periodical blood counts were done on many of the 30 cases treated with Prontosil only, but nothing abnormal was revealed except in the case of failure described.

All the cases in all 3 groups gave negative complement fixation tests, using Schering compligon antigen, both at start and finish of treatment. But in some cases of gonococcal infection, not in the series here described, some evidence, as yet small, has been obtained suggesting

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that in chronic gonococcal infections Prontosil may sometimes act to provoke a negative serum into becoming a positive one, and even provoke a urethral discharge in which gonococci are easily found. Sulphanilamide may yet prove to have a value for the processes of diagnosis.